



Cooper, Sue and Taggar, Jaspal and Lewis, Sarah and Dickinson, Anne and Whitemore, Rachel and Thornton, Jim (2014) Effect of nicotine patches in pregnancy on infant and maternal outcomes at 2 years: follow-up from the randomised, double-blind, placebo-controlled SNAP trial. *Lancet Respiratory Medicine*, 2 (9). pp. 728-737. ISSN 2213-2619

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Effect of nicotine patches in pregnancy on infant and maternal outcomes at 2 years: follow-up from the randomised, double-blind, placebo-controlled SNAP trial

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Summary

Background The SNAP (Smoking and Nicotine in Pregnancy) trial compared nicotine replacement therapy (NRT) patches with placebo in pregnant smokers; although NRT doubled cessation rates in the first 4 weeks, by delivery no differences in maternal smoking or birth outcomes were noted. As a result, NRT used in standard doses during pregnancy is considered ineffective for smoking cessation. Subsequent effects of NRT on the children of treated mothers are unknown because no trials have investigated the effect of gestational NRT use beyond birth. To assess whether NRT use in pregnancy might cause harm to infants, we aimed to compare effects of NRT and placebo on infant development 2 years after delivery.

Methods 1050 pregnant smokers aged 16–45 years, at 12–24 weeks' gestation, and smoking at least five cigarettes per day were recruited from seven hospitals in England between May 1, 2007, and Feb 26, 2010, and followed up until their infants were 2 years old. Participants were randomly assigned (1:1) via a computer-generated pseudorandom code with permuted blocks of randomly varying size to receive 8-week courses of NRT patches (15 mg/16 h) (n=521) or matched placebo (n=529); both groups received behavioural smoking cessation support. Randomisation was stratified by site with participants, health-care professionals, and research staff masked to treatment allocation. The primary results for participants and infants at delivery were published in 2012; we present results from the trial cohort 2 years after birth. After delivery, questionnaires were posted to participants and, if there was no response, to family physicians. The primary outcome at 2 years was infants' survival without developmental impairment (ie, no disability or problems with behaviour or development). Treatment groups were compared on an intention-to-treat basis. The trial is registered with Controlled-Trials.com, number ISRCTN07249128.

Findings Questionnaires were returned at 2 years for 891 (88%) of 1010 live singleton births (445 of (88%) 503 given NRT and 446 (88%) of 507 given placebo). Because of missing data, developmental outcomes, including four infant deaths, were documented for 888 of (88%) 1010 singleton infants; 445 (88%) of 503 infants in NRT group and 443 (87%) of 507 infants in placebo. In the NRT group, 323 (73%) of 445 infants had no impairment compared with 290 (65%) of 443 infants in the placebo group (odds ratio [OR] 1.40, 95% CI 1.05–1.86, p=0.023). At 2 years, 15 (3%) of 521 mothers in the NRT group and nine (2%) of 529 mothers in the placebo groups self-reported prolonged smoking abstinence since a quit date set in pregnancy (OR 1.71, 95% CI 0.74–3.94, p=0.20). Adverse events were not collected after delivery, but previously reported adverse pregnancy and birth outcomes were similar in the two groups.

Interpretation Infants born to women who used NRT for smoking cessation in pregnancy were more likely to have unimpaired development. NRT had no effect on prolonged abstinence from smoking but did cause a temporary doubling of smoking cessation shortly after randomisation during pregnancy, which could explain findings. If findings are confirmed by subsequent research, this has potential implications for the management of smoking in pregnancy.

Funding National Institute for Health Research Health Technology Assessment Programme.

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Introduction

Smoking in pregnancy is the biggest preventable cause of death and illness in women and infants and is associated with adverse pregnancy and birth outcomes.^{1,2} Despite being an international public health problem, and although the prevalence of smoking in pregnancy is generally falling in high-income countries,^{3–6} rates are rising in many low-income settings⁷ and are expected to

substantially increase the future attributable global disease burden.⁸ Additionally, rates of smoking are higher, and declines have often been smaller, in mothers who are younger or have lower socioeconomic status.^{3–5,9} Smoking in pregnancy might affect infant development and is associated with behavioural problems, attention deficit disorder,^{10,11} and reduced academic attainment in children.¹⁰

Lancet Respir Med 2014;

2: 728–37

Published Online

August 11, 2014

[http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/S2213-2600(14)70157-2)

[S2213-2600\(14\)70157-2](http://dx.doi.org/10.1016/S2213-2600(14)70157-2)

This online publication has been corrected. The corrected version first appeared at thelancet.com/respiratory on October 23, 2014

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See Online for author interview with Sue Cooper

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Nicotine replacement therapy (NRT) helps non-pregnant smokers to stop,¹² but although evidence suggests that it might help pregnant smokers to achieve short-term abstinence,¹³ compliance with NRT is generally poor and by delivery there is no longer any evidence for effectiveness.¹⁴ Previously, we reported smoking cessation outcomes from a large trial investigating the efficacy of 15 mg/16 h NRT patches used in pregnancy (the Smoking and Nicotine in Pregnancy [SNAP] trial).¹³ We reported that NRT had no effect on validated abstinence from smoking at delivery, although validated cessation rates at 1 month after randomisation were twice as high in the NRT group; no safety issues were identified, with adverse pregnancy and birth outcomes similar in the two groups.¹³

To our knowledge, no trials have investigated the effect of NRT on outcomes for children beyond delivery; thus we designed our study also to assess this. Nicotine is potentially fetotoxic.¹⁵ One theory is that nicotine from either smoking or NRT might stimulate CNS nicotinic receptors at inappropriate times during development and, consistent with this, nicotine given to pregnant rats has a negative effect on neurogenesis and synaptogenesis in the fetal CNS.¹⁵ Therefore, observed associations between parental smoking and adverse infant development could be plausible,^{10,11} and might be caused by nicotine inhalation from cigarette smoke. As a result, NRT might benefit the fetus and child by reducing exposure to smoking at crucial times for embryogenesis and infant neural development, but it may also cause harm through the negative effects of direct activation of nicotinic cholinergic receptors in the developing CNS. To assess whether NRT patches use by pregnant smokers who are trying to quit might be harmful, we compared health outcomes at 2 years between infants born in placebo group and active group from the SNAP trial.

Methods

Study design and participants

SNAP was a multicentre, double-blind, randomised, placebo-controlled, parallel-group trial that recruited 1050 pregnant smokers from seven hospital antenatal clinics in England between May 1, 2007, and Feb 26, 2010; we have previously reported the full methods and outcomes at delivery.¹³ Briefly, participants were aged 16–45 years, 12–24 weeks' gestation, smoked 10 or more cigarettes daily before pregnancy, and were smoking five or more cigarettes per day at trial enrolment, with an exhaled carbon monoxide (CO) reading of at least 8 ppm. Research midwives obtained written consent, collected baseline data, and delivered behavioural cessation support to all participants. The research midwives then entered eligibility criteria onto a secure online database.

The study was approved by Oxfordshire Research Ethics Committee A, and all participants gave written

informed consent, including access to medical records for maintaining contact and for following up theirs and their child's health status.

Randomisation and masking

Participants were randomly assigned (1:1) to receive up to 8-weeks treatment with NRT (15 mg/16 h transdermal patches) or identically packaged and visually matched placebo patches (all patches manufactured by and purchased at market rate from United Pharmaceuticals, Amman, Jordan), issued as two 4-week supplies (521 for NRT group, 529 for placebo group). Participants were instructed to start using these patches on their quit date, to remove them at night, and to only use the patches if they were not smoking. Participants were issued with the second 4-week supply of patches if they reported not smoking one month after their quit date, and this was validated with a CO reading less than 8 ppm.

Randomisation was stratified by site, and used a computer-generated pseudorandom code with permuted blocks of randomly varying size, created by Nottingham Clinical Trials Unit. All participants, site pharmacists, and research staff were masked to treatment allocation. Additionally, during the 2-year follow-up period after ascertainment of primary outcome at delivery, participants, health-care professionals, and all staff involved in collecting, entering, and classifying follow-up data remained masked. Data cleaning and preparatory work were done masked to treatment allocation, and all analyses at delivery were done masked to study group allocation, with codes broken after these were completed. However, analysis of the follow-up data was not possible in a completely blind manner, because the unblinded data from the primary trial was already available. We did not evaluate the success of masking for participants or research staff.

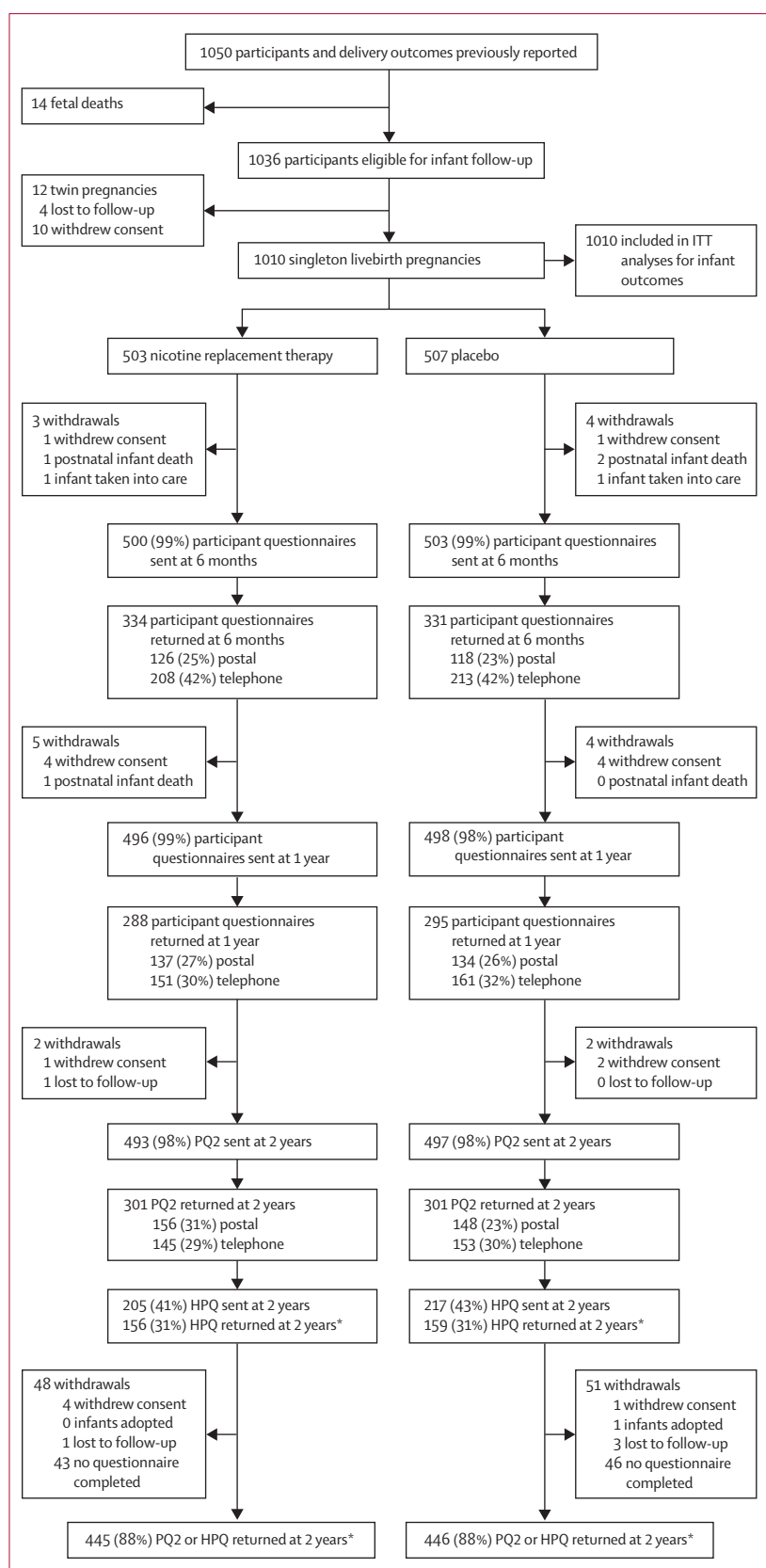
Procedures

Participants' smoking status was assessed 1 month after randomisation and at delivery, with self-reported non-smoking status validated by CO concentration, salivary cotinine (cotinine is the primary metabolite of nicotine) concentration, or both; those participants who had CO validated cessation at 1 month (<8 ppm) could receive a further 4-week supply of patches. To estimate treatment adherence, participants were asked how many study patches they had used at 1 month, 2 months (if issued with a second 4-week supply), and delivery, and if they had used any non-trial NRT.

Safety was assessed by collection of adverse pregnancy and birth outcomes from participants and medical notes.

Of 1050 pregnancies, 1034 known live births (1010 singletons, 24 twins), five miscarriages, seven stillbirths, one termination, one missed abortion, and 14 pregnancies with unknown birth outcomes were noted.¹³ Participants with known live infants were posted questionnaires at 6, 12, and 24 months after childbirth.

For more details on how items were mapped, see the **Statistical Analysis Plan** at <http://eprints.nottingham.ac.uk/3283/>



We did not send questionnaires where participants had withdrawn consent, when birth outcomes were unknown, or infants who had died either during pregnancy or after birth. At each timepoint, we sent one postal reminder and attempted telephone completion if necessary. To maintain contact, we sent greetings cards after childbirth, at Christmas, and on infant's birthdays, including postcards to inform us of address changes. We incentivised the return of completed questionnaires with a cotton bag at 1 year and a £5 shopping voucher at 2 years; we also held colouring competitions for 2-year-olds, offering £50 shopping voucher prizes. At 2 years, we sent a postal questionnaire to non-respondents' family physicians (Health Professional Questionnaire [HPQ]).

At 6, 12, and 24 months, participant questionnaires asked about maternal smoking behaviour and infants' respiratory problems. Information about hospital admissions (at all timepoints), feeding method (6 months and 12 months), and EuroQol (EQ-5D; 6 months)¹⁶ were also collected, but are not reported here. The 24-month participant questionnaire (PQ2) included five domains of the Ages and Stages Questionnaire 3rd edition (ASQ-3)¹⁷ (communication, gross motor, fine motor, problem solving, and personal-social development); with permission, wording was slightly anglicised. Seven additional PQ2 items (six from the ASQ-3) investigated general and specific parental concerns about infant development. The HPQ, derived from a questionnaire used in a similar study,¹⁸ was designed for completion with medical or health visitor records; items were consistent with PQ2, and hence ASQ-3, and aimed to measure children's disability and health (questionnaires can be requested from corresponding author).^{19–21}

Participants' Index of Multiple Deprivation (IMD) scores were attributed by linkage of postal codes with routine English Local Government data;²² a higher score indicates more deprivation.

Outcomes

All of the outcomes were binary—ie, participants or infants were defined as either having the outcome or not.

PQ2 and HPQ responses were combined to derive the primary 2-year outcome, which was survival with no impairment. This was survival without either of two prespecified developmental outcomes; developmental and behavioural problems or disability. Details of how PQ2 and HPQ items were mapped to these outcomes can be found online in the Statistical Analysis Plan. Because high rates of disability or developmental

Figure: Derivation of the 1010 live singleton births from 1036 pregnancies and completeness of infants' follow-up to 2 years

ITT=intention to treat. PQ2=24-month participant questionnaire. HPQ=health professional questionnaire. *26 HPQs were returned in participants who had already returned a PQ2 (12 for NRT, 14 for placebo) and these were not included in subsequent analyses.

problems were not expected, combination of outcomes provided a clinically meaningful measure of harm, with increased study power for detection of harm from NRT, and reduced problems arising from multiple testing. Appendix pp 5–6 provides separate results for each of the ASQ domains. For cases where both PQ2 and HPQ were returned, only PQ2 data were used.

Details of how the absence, presence, or severity of impairment was determined from HPQ or PQ2 responses can be found online in the Statistical Analysis Plan. In brief, with the PQ2, infants were deemed to have survived with no impairment if scores, derived with standard methods for the five ASQ-3 domains, were above accepted thresholds indicating normal development¹⁷ and responses to other, non-domain, ASQ-3 items also indicated no problems. For children with HPQ returns only, this criterion was met if no responses indicated developmental problems. In cases for which scores and other responses indicated potential impairments, two further mutually-exclusive categories were allocated: definite and suspected developmental impairment. Infants were classified as having definite impairment when their ASQ-3 scores were at or below the published cut-point in any of the domains, or the HPQ responses indicated severe disability or developmental delay. Suspected impairment was used for cases in which one or more of the ASQ-3 scores fell within the questionnaire's borderline range, or if other responses from either the PQ2 or HPQ were judged by a clinical member of the research team to potentially indicate developmental impairment or disability. Determination of impairment category by this clinician was done masked to treatment allocation.

Infants were classed as having a respiratory problem when indicated by any item on either the PQ2 or HPQ. Similar to developmental problems, responses were combined to avoid multiple testing and to maximise power, but individual results are provided in appendix pp 7–8.

At all points, participants reported whether they had smoked in the last week, and if they had abstained from smoking since delivery, with allowance for smoking on up to five occasions.²³ Prolonged abstinence from smoking since the quit date set during pregnancy was defined as validated abstinence at delivery, plus reported abstinence since delivery at every follow up.

Statistical analysis

Sample size for the trial was determined for the previously reported primary outcome of smoking cessation rate at delivery.¹³ Within those participants available at follow-up, baseline maternal characteristics and birth outcomes were compared between trial groups; the same characteristics were also compared in those who had outcomes determined by PQ2, HPQ, or who were lost to follow-up at 2 years. Statistical analyses were

done with Stata/SE version 11.2 (StataCorp LP, College Station, TX, USA).

	NRT	Placebo
Maternal characteristics at study enrolment; n=448 for NRT, n=452 for placebo*		
Age (years)	26.5 (6.2)	26.3 (6.1)
Number of cigarettes smoked daily before pregnancy	20 (15–20)	20 (15–20)
Number of cigarettes smoked daily at baseline	13 (10–20)	15 (10–20)
Gestational age at baseline (weeks)	16.2 (3.5)	16.3 (3.5)
Ethnic origin		
White British	434 (97%)	442 (98%)
Other	14 (3%)	10 (2%)
Age when left full time education (years)	16.2 (1.4)	16.3 (1.7)
Missing data (n)	5	8
Index of multiple deprivation	32.1 (16.7)	32.4 (16.9)
Missing data (n)	13	9
Parity		
0–1	306 (68%)	311 (69%)
2–3	111 (25%)	121 (27%)
≥4	31 (7%)	20 (4%)
Salivary cotinine at baseline (ng/mL)	123.7 (80.2–185.4)	120.9 (75.6–175.9)
Missing data (n)	35	33
Time from waking to first cigarette (min)		
0–15	245 (55%)	243 (54%)
16–60	169 (38%)	168 (37%)
>60	34 (8%)	34 (8%)
Women with partner who smokes	306 (68%)	306 (68%)
Missing data (n, %)	34 (8%)	38 (8%)
Height (cm)	162.9 (6.8)	163.1 (6.4)
Missing data (n)	12	13
Weight (kg)	71.2 (17.8)	72.3 (17.1)
Missing data (n)	8	8
Previous preterm birth	38 (8%)	42 (9%)
Length of first behavioural support session		
<30 min	66 (15%)	67 (15%)
31–60 min	376 (84%)	371 (82%)
>60 min	6 (1%)	14 (3%)
Use of NRT earlier in pregnancy	19 (4%)	23 (5%)
Maternal smoking outcomes at delivery; n=448 for NRT, n=452 for placebo*		
Met primary smoking cessation outcome	46 (10%)	37 (8%)
Infant birth outcomes at delivery; n= 445 for NRT, n=446 for placebo†		
Birthweight, unadjusted (kg)	3.2 (0.6)	3.2 (0.6)
Gestational age (weeks)	39.5 (2.1)	39.5 (2.2)
Preterm birth	36 (8%)	40 (9%)
Low birthweight (<2.5 kg)	49 (11%)	37 (8%)
Neonatal intensive-care unit admission	29 (7%)	32 (7%)
Apgar score at 5 min <7	12 (3%)	13 (3%)
Congenital abnormalities	7 (2%)	12 (3%)
Infant on ventilator >24 h	8 (2%)	10 (2%)
Assisted vaginal delivery	33 (7%)	37 (8%)
Delivery by caesarean section	90 (20%)	69 (15%)

Data are n (%), median (range), or mean (SD). NRT=nicotine replacement therapy. *All pregnancies (ie, includes twins). †Singleton pregnancies only.

Table 1: Comparison of maternal characteristics and birth outcomes for participants who provided data at 2 years

For more details on how impairment was determined, see the **Statistical Analysis Plan** at <http://eprints.nottingham.ac.uk/3283/>

Separate multivariable analyses were done for presence or absence of every outcome, including the primary outcome (survival with no impairment), and for secondary outcomes (definite impairment, respiratory

problems, and maternal smoking behaviour). For 2-year outcomes, treatment groups were compared on an intention-to-treat basis. Infant outcomes were only compared for pregnancies that were known to have resulted in live births. Pregnancies that ended in fetal death before birth (eg, miscarriage, stillbirth, or elective termination), and those for which the pregnancy outcome was unknown did not contribute to analyses, but postnatal infant deaths were included in the denominator for developmental outcomes. We did the primary analysis within singleton births, because non-independent, multiple births might have worse birth outcomes than singletons. We then compared results with those obtained after multiple imputation to deal with missing values. Multiple imputation was done with mi commands in Stata, including complete baseline variables, smoking status at delivery, and treatment allocation in the imputation model (20 imputations). Treatment effects were estimated from imputed datasets with logistic regression adjusted for centre as the stratification factor. We then did two further analyses; a complete case analysis including multiple births allowing for clustering,²⁴ and a further full population analysis with parent PQ2 questionnaires only.

In a prespecified secondary analysis, we used logistic regression to explore the dose–response relation between self-reported adherence with nicotine patches¹³ and, as a dependent variable, infants' survival without impairment. For this analysis, three categories were created: zero adherence (ie, allocated placebo patch or reported zero nicotine patches used) and, for participants reporting use of at least one nicotine patch, two categories representing above and below the median reported adherence of 10 nicotine patches (ie, 1–10 and 11–56 days adherence).

Smoking outcomes for the treatment groups at 6, 12, and 24 months were compared on an intention-to-treat basis, with non-respondents assumed to smoke. Logistic regression, adjusted for centre, provided odds ratios for the treatment effect, and a sensitivity analysis adjusted for baseline salivary cotinine, partner's smoking status, and age at finishing education was done. Finally, a sensitivity analysis investigated the effect on findings of alternatives to the assumption that those with missing data were smokers.²⁵

The trial is registered with Controlled-Trials.com, number ISRCTN07249128.

Role of the funding source

The funders of this study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. SC, JT, SL, and TC had full access to the data in the study. SC and TC had the final responsibility for the decision to submit for publication.

Results

Follow-up was completed by Dec 14, 2012. The figure shows the derivation of the 1010 live singleton births

	Followed up (PQ2; n=606)	Followed up (HPQ; n=294)*	Not followed up (n=150)†
Maternal characteristics at enrolment/randomisation (all pregnancies)			
Age (years)	26.9 (6.3)	25.5 (5.6)	25.7 (6.3)
Cigarettes smoked daily before pregnancy	20 (15–20)	20 (15–20)	20 (15–20)
Cigarettes smoked daily at baseline	15 (10–20)	15 (10–18)	12 (10–15)
Gestational age at baseline (weeks)	16.2 (3.5)	16.4 (3.5)	16.2 (3.6)
Ethnic origin			
White British	588 (97%)	288 (98%)	142 (95%)
Other	18 (3%)	6 (2%)	8 (5%)
Age left full time education (years)	16.3 (1.7)	16.2 (1.3)	16.3 (1.5)
Index of Multiple Deprivation	32.3 (17.1)	32.2 (16.2)	36.8 (16.0)
Parity			
0–1	424 (70%)	193 (66%)	102 (68%)
2–3	144 (24%)	88 (30%)	39 (26%)
≥4	38 (6%)	13 (4%)	9 (6%)
Salivary concentration level at baseline (ng/mL)	119.1 (72.1–179.5)	131.6 (88.7–184.7)	119.1 (80.0–161.3)
Time from waking to first cigarette			
0–15 min	329 (54%)	159 (54%)	78 (52%)
16–60 min	231 (38%)	106 (36%)	60 (40%)
>60 min	46 (8%)	29 (10%)	12 (8%)
Women with partner who smokes	408 (67%)	204 (69%)	104 (69%)
Height (cm)	162.9 (6.8)	163.2 (6.3)	163.7 (7.0)
Weight (kg)	72.4 (16.6)	70.5 (19.1)	71.0 (18.9)
Previous preterm birth	47 (8%)	33 (11%)	12 (8%)
Length of first behavioural support session			
<30 min	87 (14%)	46 (16%)	32 (21%)
31–60 min	505 (83%)	242 (82%)	114 (76%)
>60 min	14 (2%)	6 (2%)	4 (3%)
Use of NRT earlier in pregnancy	33 (5%)	9 (3%)	5 (3%)
Maternal smoking at delivery (all pregnancies)			
Met primary smoking cessation outcome	66 (11%)	17 (6%)	6 (4%)
Infant birth outcomes (singleton pregnancies; n=602 for PQ2, n=289* for HPQ, n=119 for not followed up)			
Birthweight, unadjusted (kg)	3.2 (0.58)	3.1 (0.62)	3.2 (0.60)
Gestational age (weeks)	39.5 (2.1)	39.4 (2.3)	39.6 (2.1)
Preterm birth	46 (8%)	30 (10%)	9 (8%)
Low birthweight (<2.5 kg)	46 (8%)	40 (14%)	13 (11%)
NICU admission	39 (6%)	22 (8%)	7 (6%)
Apgar score at 5 min <7	13 (2%)	12 (4%)	9 (8%)
Congenital abnormalities	8 (1%)	11 (4%)	3 (3%)
Infant on ventilator >24 h	11 (2%)	7 (2%)	3 (3%)
Assisted vaginal delivery	51 (8%)	19 (7%)	11 (9%)
Delivery by caesarean section	118 (20%)	41 (14%)	25 (21%)

Data are n (%), median (range), or mean (SD). PQ2=24-month participant questionnaire. HPQ=health professional questionnaire (also at 24 months). NRT=nicotine replacement therapy. *26 participants who provided both HPQ and PQ2 data were excluded from this analysis (n=12 for NRT, n=14 for placebo, all singleton pregnancies). †Includes participants who experienced fetal or infant death (n=18), whose pregnancy outcome was unknown (n=14), and those who withdrew, were lost to follow-up or did not return questionnaires at 24 months (n=118).

Table 2: Maternal and infant characteristics—comparison of participants and singleton infants for whom outcome data was and was not available at 2 years

	NRT	Placebo	Complete case analysis (singleton pregnancies)**		Complete case analyses (adjusted for clustering by twin pregnancies)†††‡		Multiple imputation ITT analyses (singleton births; n=1010)	
			OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Number of respondents*	445	446						
Number with development outcomes documented†	443	441
Number of infant deaths (after delivery)	2	2
Number with known developmental outcomes	445	443
Survival with no impairment‡	323/445 (73%)	290/443 (65%)	1.41 (1.05–1.87)	0.0202	1.43 (1.08–1.91)	0.013	1.40 (1.05–1.86)	0.023
Definite developmental impairment§	48/445 (11%)	64/443 (14%)	0.71 (0.48–1.06)	0.09	0.73 (0.49–1.09)	0.13	0.71 (0.47–1.09)	0.12
Suspected development impairment (%)¶	72/445 (16%)	87/443 (20%)
Number with respiratory outcomes documented†	444	444
Respiratory problems	132/444 (30%)	111/444 (25%)	1.28 (0.95–1.73)	0.10	1.32 (0.98–1.77)	0.07	1.30 (0.97–1.74)	0.08

Data are n or n (%). NRT=nicotine replacement therapy. ITT=intention to treat. OR=odds ratio. *Participants with singleton livebirths with a response to either questionnaire (24-month participant questionnaire [PQ2] or health professional questionnaire [HPQ]) at 2-year follow-up. †Because of missing data, developmental outcomes were not documented for seven participants (n=2 for HPQ in NRT group; n=1 for PQ2, n=4 for HPQ in placebo). Because of missing data, respiratory outcomes could not be determined for three participants (n=1 for HPQ in NRT group; n=1 for PQ2, n=1 for HPQ in placebo). ‡Score above borderline score in ASQ-3 for all domains, and no problems reported in additional sections of ASQ-3 (ie, any hearing, talking, understanding, neuromotor or vision problems). §ASQ-3 score equal to or below cutpoint in ≥1 domain, HPQ indicates severe disability and/or severe developmental delay. ¶ASQ-3 borderline score in ≥1 domain, but no scores equal to or below cut-point, and/or judged to have mild/moderate or possible impairment, disability or development delay from the additional questions on the PQ2 and/or HPQ including problems with hearing, speech, neuromotor, vision, behaviour, or feeding problems. ||Any report of respiratory symptoms, asthma diagnosis, asthma medications, or admissions to hospital for respiratory problems at 2-year follow-up; this denominator does not include postnatal infant deaths because it is not possible to attribute these infants with a respiratory outcome. **Because of missing data, denominators were different for each outcome; total infants with known developmental outcomes (including postnatal infant deaths) was 888 (445 plus 443); total infants with known respiratory outcomes (excluding postnatal infant deaths) was 888 (444 plus 444). ††Infants from nine twin pregnancies returned a PQ2 or HPQ (n=6 for NRT, n=12 for placebo). ‡‡Because of missing data, denominators were different for each outcome: total infants (including twins) with known developmental outcomes (including postnatal deaths) was 906 (451 plus 455); total infants (including twins) with known respiratory outcomes (excluding postnatal infant deaths) was 906 (450 plus 456).

Table 3: Infant development and respiratory outcomes at 2 years compared between treatment groups

from 1036 pregnancies and completeness of infants' follow-up to 2 years (appendix p 2). Of singleton infants, 891 (88%) participants returned a PQ2 or HPQ; 445 (88%) of 503 infants given NRT and 446 (88%) of 507 infants given placebo. 26 (3%) of 990 participants were late returning their PQ2, and an HPQ had also been sent and returned; the PQ2 was our primary source of data and so these 26 HPQs were not analysed. Because of missing data, development outcomes were only attributable for 443 infants in the NRT group and 441 infants in the placebo group (including four postnatal infant deaths [two for NRT, two for placebo]) and respiratory outcomes for 444 infants in the NRT group and 444 infants in the placebo group.

Of participants and singleton infants with 2-year outcome data, baseline characteristics and birth outcomes in the NRT and placebo groups were generally similar (table 1). These comparison groups at 2 years also had similar characteristics to those previously reported in the full trial cohort.¹³ At 2 years, as seen at delivery, more births by caesarean occurred in the NRT group than in the placebo group (table 1). The proportion of mothers at 2 years who had had validated abstinence from smoking at delivery (table 1) was again comparable to those in the full cohort (49 [9%] of 521 mothers in the NRT group and 40 [8%] of 529 in the placebo group).¹³

Table 2 shows a comparison of characteristics between participants who returned PQ2s, those for whom HPQs were completed, and those lost to follow-up. The mean IMD score was higher in those participants who were not followed up compared with that for PQ2 and for HPQ

(table 2), but most differences between the groups' baseline characteristics or birth outcomes were minor. Breast-feeding rates reported at 6 months were very similar in the two groups; 133 (40%) of 330 respondents in the NRT group reported breastfeeding exclusively immediately after childbirth compared with 126 (38%) of 333 in the placebo group, and by 6 months these rates had fallen to 14 (4%) participants for NRT and 10 (3%) for placebo.

Table 3 shows infant developmental and respiratory outcomes by treatment groups for all those participants with known outcomes, including four postnatal deaths. Infants born to women receiving NRT were significantly more likely to have survived with no impairment than those receiving placebo (table 3). In the ITT analysis with multiple imputation, the primary outcome was significantly more common in the NRT than in the placebo group (table 3). Findings from complete case analyses of singleton pregnancies only and adjusted for clustering by twin pregnancies (table 3), and from similar analyses of just PQ2 responses (excluding postnatal deaths) (appendix p 3), were very similar. For example, in the complete case analysis of PQ2 responses for singleton infants, the difference in primary outcomes between groups was comparable to that in the main analysis (OR 1.52, 95% CI 1.09–2.11, $p=0.0124$; appendix p 3). Analyses of individual ASQ-3 domains showed effects of similar size and direction, although only differences in the personal social domain reached statistical significance. Findings from comparison of scores on individual domains were: fine motor skills (OR 1.30, 95% CI 0.82–2.08, $p=0.27$), gross motor skills (1.40, 0.87–2.22,

	NRT (n=521)*	Placebo (n=529)*	Adjusted for centre only		Adjusted‡	
			OR (95% CI)†	p value	OR (95% CI)	p value
6 months after delivery						
Respondents	335 (64%)	338 (64%)
Self-reported prolonged abstinence since delivery§	57 (11%)	50 (9%)	1.18 (0.79–1.76)	0.43	1.23 (0.81–1.87)	0.33
Self-reported 7 day cessation (%)	56 (11%)	52 (10%)	1.11 (0.74–1.65)	0.62	1.15 (0.76–1.74)	0.50
Prolonged abstinence from smoking between quit date and 6 months after delivery¶	28 (5%)	17 (3%)	1.71 (0.92–3.17)	0.08	1.84 (0.98–3.46)	0.0547
1 year after delivery						
Respondents	288 (55%)	300 (57%)
Self-reported prolonged abstinence since delivery§	33 (6%)	29 (5%)	1.16 (0.70–1.95)	0.56	1.18 (0.69–2.04)	0.54
Self-reported 7 day cessation	55 (11%)	37 (7%)	1.57 (1.01–2.43)	0.0413	1.55 (0.98–2.46)	0.06
Prolonged abstinence from smoking between quit date and 1 year after delivery¶	19 (4%)	11 (2%)	1.78 (0.84–3.78)	0.13	2.20 (0.98–4.92)	0.0475
2 years after delivery						
Respondents (PQ2 only)**	302 (58%)	304 (57%)
Self-reported prolonged abstinence since delivery§	23 (4%)	21 (4%)	1.11 (0.61–2.04)	0.73	1.03 (0.53–1.98)	0.94
Self-reported 7 day cessation	45 (9%)	43 (8%)	1.06 (0.69–1.65)	0.78	0.98 (0.62–1.56)	0.95
Prolonged abstinence from smoking between quit date and 2 years after delivery¶	15 (3%)	9 (2%)	1.71 (0.74–3.94)	0.20	1.96 (0.82–4.70)	0.12

Data are n (%), unless otherwise indicated. NRT=nicotine replacement therapy. OR=odds ratio. PQ2=24-month participant questionnaire. *For the smoking outcomes, participants who did not provide data or were lost to follow-up are assumed to be smokers and included in the denominator. †Adjusted for centre only (as a stratification factor). ‡Adjusted for centre, salivary cotinine concentration at baseline, partner's smoking status, and age at leaving full time education. §Self-reported prolonged abstinence since delivery in the table suggests the participant smoked less than five times since baby was born. ¶Participant met criteria for prolonged abstinence at delivery (ie, positive primary outcome) plus self-reported smoking less than five times since baby was born. ||Cessation information was collected at 1 year, but was not listed as an outcome in the protocol. **Smoking status was only ascertained in the PQ2.

Table 4: Maternal smoking outcomes at 6 months, 1 year, and 2 years after delivery

p=0.15), communication (1.21, 0.75–1.96, p=0.43), problem solving (1.34, 0.90–2.01, p=0.15), personal social (1.64, 1.08–2.48, p=0.0184; appendix p 5). The results showed a dose–response relation between use of NRT patches in pregnancy and infant outcomes at 2 years compared with infants born to participants who did not use nicotine patches, but we noted no difference in outcomes of infants born to women who reported using between one and 10 NRT patches (appendix p 9). However, those infants born to women who reported using between 11 and 56 NRT patches were more likely to have no impairments (OR [adjusted for partner smoking status] 1.72, 95% CI 1.22–2.57, p=0.004).

Combined respiratory outcomes could be attributed for 888 of the singleton infants; 444 infants in the NRT group and 444 infants in the placebo group; of which 132 (30%) in the NRT group and 111 (25%) in the placebo group reported respiratory problems (table 3); further breakdown of respiratory outcomes is shown in appendix pp 7–8).

For smoking outcomes, response rates at the three timepoints are shown in table 4, and are for all 1050 randomised women. Response rates were around 64% at 6 months, falling slightly to 58% at 2 years; these are lower than those for the developmental and respiratory outcomes as the smoking questions were only included in the participant questionnaires. After delivery, abstinence from smoking was low, and the relapse rate gradually increased (table 4). Slightly more participants reported not smoking in the NRT group than placebo at each timepoint, but none were significantly different (table 4). By 2 years

after delivery, 15 (3%) participants allocated NRT and nine (2%) allocated placebo remained abstinent (table 4); the sensitivity analysis noted that varying the assumptions made that those with missing data were all smokers had almost no effect on this effect size.

Additional adverse events were not collected after delivery, but previously reported adverse pregnancy and birth outcomes were similar in the two groups.¹³

Discussion

At 2 years of age, infants born to women who had been allocated to receive NRT in pregnancy were more likely to have survived without developmental impairments than those in the placebo group, but no differences in the frequency of respiratory problems were noted (panel). NRT had only minor effects on smoking cessation, with very low prolonged abstinence rates 2 years after delivery. To our knowledge this is the first time a trial has reported the effect of a smoking cessation intervention in pregnancy on infant outcomes beyond delivery, and also the first time that maternal smoking rates within trial groups have been reported longer than 18 months after childbirth.

Using rigorous methods to maintain contact with participants, we achieved high outcome ascertainment rates, with low rates of withdrawal and missing data. In conjunction with staff doing the follow-up being masked to treatment allocation, this might account for the similar baseline characteristics of the two groups and the absence of systematic differences between those lost to follow-up and those included in analyses (tables 1, 2). Multiple imputation included complete baseline variables, smoking

status at delivery, and treatment allocation in the model and so should satisfactorily adjust for the minor differences in baseline characteristics of respondents such as mode of delivery; hence findings from the analyses presented are likely to be internally valid.

A medically qualified researcher, masked to treatment allocation, manually checked all free-text responses on the outcome questionnaires and, if these generated uncertainty about either the presence or gravity of impairment, this was categorised as suspected, rather than definite or no impairment. This approach was also taken with respiratory item responses. The similar pattern of findings across all pre-planned analyses, irrespective of data sources used, suggests consistent allocation of outcomes.

The ASQ-3, which was the basis of our parent-completed questionnaire, is a screening instrument designed to accurately identify children with developmental problems and so avoid over-referrals and under-referrals for further assessment.¹⁷ In a comparable setting, when compared with such subsequent assessments, a similar earlier version of the ASQ had a sensitivity of 87·4% (specificity 82·3%).³² Although this sensitivity suggests that our outcome measure will have had good discrimination, some impaired infants will probably not have been detected and some non-impaired infants will have been wrongly labelled as impaired; face-to-face assessment would have been more accurate. However, the masking of respondents and outcome assessors make it unlikely that trial groups will have had different rates of outcome misclassification. Factors that were not measured, such as nutrition or environment, could have affected childhood development; however, this was a large randomised, blinded trial that was well-balanced for most characteristics that were collected. Developmental impairment is a fairly common outcome and, like all studies that use OR for an outcome that is not rare, our OR estimates might overestimate the risk ratio. Nevertheless, the observed difference in developmental outcomes between trial groups is likely to be real and meaningful.

We assumed that all participants without smoking outcome data were smokers. Results of analyses investigating the effects of different associations between smoking behaviour and being lost to follow up showed that alternative assumptions did not change the findings; however, because smoking outcomes after delivery were not validated, actual prolonged quit rates could be even lower. Although we report data for maternal smoking status at 6 months, 1 year, and 2 years (table 4), data collected did not include cumulative number of cigarettes smoked, which would have been useful for assessment of whether or not NRT resulted in reduced smoking either during use or after its discontinuation. Nevertheless, because we note a significant difference in validated quit rates 1 month after randomisation, which was reported in our previous paper (OR 2·10, 95% CI 1·49–2·97),¹³ we do know that those in the NRT group had reduced their

Panel: Research in context

Systematic review

When planning this trial, a published Cochrane review was consulted.²⁶ This systematic review established that at the outset of our trial (Feb 1, 2006), only three randomised controlled trials^{27–29} had investigated the use of nicotine replacement therapy (NRT) for smoking cessation in pregnancy, with no evidence from these that NRT was effective to help pregnant women stop smoking. Additionally, none of these trials had monitored maternal smoking rates after delivery or child outcomes such as respiratory symptoms or developmental impairment. More recently, two Cochrane reviews, including one authored by some of the SNAP team, have collated trials investigating pharmacological¹⁴ and psychosocial cessation³⁰ interventions in pregnancy, and neither includes any studies that report infant outcomes beyond delivery. Evidence-based WHO guidance on smoking in pregnancy similarly showed no studies of smoking cessation during pregnancy that addressed infant outcomes, and recommended further research on the safety of pharmacotherapeutic cessation drugs.³¹

Interpretation

To our knowledge, this is the first time a trial has tested the effects of a smoking cessation intervention delivered in pregnancy on infant outcomes. We showed that NRT used for smoking cessation during pregnancy resulted in better infant developmental outcomes. These improved outcomes could have been caused by reduced maternal smoking during pregnancy, even though, overall, NRT was not considered effective for prolonged cessation. This finding should be further evaluated through reassessment of the infants of the SNAP trial in later childhood.

smoking more than those in the placebo group for at least 4 weeks during the second trimester—an important period in embryo development. Additionally, before 2 years of age, most infant exposure to environmental tobacco smoke (ETS) is domestic and attributable to parental smoking;³³ as a result, data for maternal smoking are likely to reflect infants' exposure to ETS and the design of the study is such that any biases in reporting of smoking habits would affect both groups similarly. Unfortunately, after delivery, we collected no further biochemical measures of maternal smoking and no biomarkers of tobacco smoke exposure were obtained directly from the infants in the study, and so we cannot make any definitive conclusions about infants' exposure to ETS. Additionally, we acknowledge that participant recall or report of smoking might be inaccurate; however, there is no reason to believe that this will be different between the groups. Also, we did not collect any data for alcohol intake during pregnancy, but because other baseline characteristics were similar we do not suspect that this would have been different between the two groups.

We did not anticipate finding better outcomes in the infants in the NRT group; however, although less

impairment was noted in children of mothers who reported greater than median adherence with nicotine patches, findings from this analysis should be considered exploratory. The observed dose–response relation could suggest a real effect, attributable to NRT, but equally, alternative explanations might exist. For example, this analysis does not take into account the fact that people who adhere with treatments might differ (eg, in lifestyle and health behaviours) from those who do not, and improved infant outcomes might have occurred because of differences other than the nicotine contained in the transdermal patches used in the trial. A direct beneficial effect of nicotine on the developing fetus seems unlikely because animal studies suggest this might be toxic;^{15,34} however, animal studies might not be directly relevant to human beings and positive effects from nicotine cannot be ruled out. Benefit might also have been mediated through reduced maternal smoking, although as the limitations noted suggest, this cannot be definitively proven from our data. Smoking in pregnancy has recently been reported to have a dose–response relation with conduct problems in offspring, an association that seems independent of either maternal characteristics or those of the child-rearing environment, including exposure to tobacco smoke after birth.³⁵ Most neurons are thought to develop in the first two trimesters of pregnancy, with interconnections between these becoming organised between 24 weeks and term, however further maturation of these connections continues during the first 2 years after birth and beyond,³⁶ and fetal cerebral growth continues into late pregnancy.³⁷ However, smaller brain volumes are associated with fetal exposure to maternal smoking³⁸ and it is feasible that normal brain developmental processes were disproportionately affected in foetuses in the placebo group. Different mechanisms underpin fetal lung development, which might explain the absence of effect on respiratory outcomes. A similar, but smaller, placebo-controlled trial by Wisborg and colleagues²⁷ noted lower cotinine concentrations in mothers in the NRT group and significantly higher birthweight in the NRT group. The trial also reported that NRT had no effect on abstinence throughout pregnancy. Superficially, these findings could also seem to support the notion that NRT might reduce smoking enough to improve neonatal outcomes, even in the absence of an effect on sustained cessation. However, because differences in cotinine concentrations and smoking rates between trial groups in late pregnancy were both non-significant, with much missing data for cotinine, and because no markers that are specific to tobacco smoke rather than NRT exposure were collected, we prefer not to hypothesise about potential reductions in fetal exposure to tobacco smoke in that study. Although such reductions remain a possibility, similar birthweight differences have not been consistently observed across other trials of NRT used for smoking cessation in pregnancy.¹⁴

The hypothesis that the NRT effects were mediated through reduced smoking is consistent with evidence that smoking during pregnancy adversely affects human brain development.³⁹ Little evidence supports an alternative hypothesis that, when compared with smoking in pregnancy, nicotine has a directly beneficial effect; however both hypotheses require further investigation because confirmation of either has potentially major implications for the management of smoking in pregnancy.

Contributors

All authors made substantial contributions to the conception and design, to the acquisition of data, or to the analysis and interpretation of data. SC was involved in study design, study conduct, acquisition of data, data analysis and interpretation of data, and writing of the report. JT did the statistical analyses, and was involved in interpretation of data and writing of the report. SL was involved in study design, study conduct, data analysis, data interpretation, and writing of the report. NM was involved in study design, study conduct, data analysis, data interpretation, and writing of the report. AD was involved in study design, study conduct, data acquisition, and writing of the report. RW was involved in study design, study conduct, data acquisition, and writing of the report. TC (SNAP Trial Chief Investigator) was involved in study design, study conduct, data analysis, data interpretation, and writing of the report. All authors were involved in drafting and revising the report and approved the final version.

Declaration of interests

NM reports personal fees from Novartis and Shire outside of the submitted work. TC reports grants from NIHR Health Technology Assessment Programme during the conduct of the study and personal fees from Pierre Fabre Laboratories (PFL), Castres, France, outside of the submitted work. All other authors declare no competing interests.

Acknowledgments

Views and opinions expressed in this Article are those of the authors and do not necessarily reflect those of the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme, the NIHR, the National Health Service or the English Department of Health. The trial was supported by a grant from the NIHR HTA Programme (project number 06/07/01). SC, SL, and TC are members of the UK Centre for Tobacco and Alcohol Studies (UKCTAS). We gratefully acknowledge funding from the British Heart Foundation, Cancer Research UK, the Economic and Social Research Council, the Medical Research Council, and the National Institute of Health Research, under the auspices of the UK Clinical Research Collaboration. SC, JT, AD, RW, and TC are members of the NIHR School for Primary Care Research. TC acknowledges the support of the East Midlands Collaboration for Leadership in Applied Health Research and Care (CLAHRC). NM receives part funding from the Department of Health's NIHR Biomedical Research Centre's funding scheme at UCLH/UCL.

References

- Green NS, Damus K, Simpson JL, et al. Research agenda for preterm birth: recommendations from the March of Dimes. *Am J Obstet Gynecol* 2005; **193**: 626–35.
- Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* 2008; **359**: 61–73.
- The NHS Information Centre. Infant Feeding Survey 2010: early results. The National Health Service Information Centre for Health and Social Care, 2011. <http://www.hscic.gov.uk/catalogue/PUB00648/inf-a-seed-serv-2010-earl-resu-rep.pdf> (accessed July 30, 2014).
- Ekblad M, Gissler M, Korkeila J, Lehtonen L. Trends and risk groups for smoking during pregnancy in Finland and other Nordic countries. *Eur J Public Health* 2013; published online Sept 13. DOI:10.1093/eurpub/ckt128.
- Mohsin M, Bauman AE, Forero R. Socioeconomic correlates and trends in smoking in pregnancy in New South Wales, Australia. *J Epidemiol Community Health* 2011; **65**: 727–32.

- 6 Centers for Disease Control and Prevention (CDC). Smoking during pregnancy—United States, 1990–2002. *MMWR Morb Mortal Wkly Rep* 2004; **53**: 911–15.
- 7 Oncken CA, Dietz PM, Tong VT, et al. Prenatal tobacco prevention and cessation interventions for women in low- and middle-income countries. *Acta Obstet Gynecol Scand* 2010; **89**: 442–53.
- 8 WHO. WHO Report on the Global Tobacco Epidemic, 2008—the MPOWER package. Geneva: World Health Organisation, 2008.
- 9 Cnattingius S. The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics, and pregnancy outcomes. *Nicotine Tob Res* 2004; **6**: S125–40.
- 10 Batstra L, Hadders-Algra M, Neeleman J. Effect of antenatal exposure to maternal smoking on behavioural problems and academic achievement in childhood: prospective evidence from a Dutch birth cohort. *Early Hum Dev* 2003; **75**: 21–33.
- 11 Thapar A, Fowler T, Rice F, et al. Maternal smoking during pregnancy and attention deficit hyperactivity disorder symptoms in offspring. *Am J Psychiatry* 2003; **160**: 1985–89.
- 12 Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2008; **1**: CD000146.
- 13 Coleman T, Cooper S, Thornton JG, et al. A randomized trial of nicotine-replacement therapy patches in pregnancy. *N Engl J Med* 2012; **366**: 808–18.
- 14 Coleman T, Chamberlain C, Davey M-A, Cooper SE, Leonardi-Bee J. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev* 2012; **9**: CD010078.
- 15 Dempsey DA, Benowitz NL. Risks and benefits of nicotine to aid smoking cessation in pregnancy. *Drug Safety* 2001; **24**: 277–322.
- 16 Kind P, Dolan P, Gudek C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ* 1998; **316**: 736–41.
- 17 Squires J, Twombly E, Bricker D, Potter L. ASQ-3 User's Guide for the Ages and Stages Questionnaires 3rd edn. Baltimore: Paul H Brookes Publishing; 2009.
- 18 Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med* 2000; **343**: 378–84.
- 19 Anon. Disability and Perinatal Care: report of two working groups. Oxford: NPEU and Oxford HA; 1995.
- 20 Jones HP, Guillea ZE, Stewart JH, Cartledge PH. The Health Status Questionnaire: achieving concordance with published disability criteria. *Arch Dis Child* 2002; **86**: 15–20.
- 21 Marlow N. Pulmonary outcomes for the extremely preterm infant. *Biol Neonate* 2000; **78**: 239–40.
- 22 Department for Communities and Local Government. English indices of deprivation, 2010. <https://www.gov.uk/government/publications/english-indices-of-deprivation-2010> (accessed July 1, 2014).
- 23 West R, Hajek P, Stead L, et al. Outcome criteria in smoking cessation trials: proposal for a common standard. *Addiction* 2005; **100**: 299–303.
- 24 Gates S, Brocklehurst P. How should randomised trials including multiple pregnancies be analysed? *BJOG* 2004; **111**: 213–19.
- 25 Hedeker D, Mermelstein RJ, Demirtas H. Analysis of binary outcomes with missing data: missing = smoking, last observation carried forward, and a little multiple imputation. *Addiction* 2007; **102**: 1564–73.
- 26 Lumley J, Oliver SS, Chamberlain C, Oakley L. Interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev* 2004; **4**: CD001055.
- 27 Wisborg K, Henriksen TB, Jespersen LB, Secher NJ. Nicotine patches for pregnant smokers: a randomized controlled study. *Obstet Gynecol* 2000; **96**: 967–71.
- 28 Kapur B, Hackman R, Selby P, Klein J, Koren G. Randomized, double-blind, placebo-controlled trial of nicotine replacement therapy in pregnancy. *Curr Ther Res Clin Exp* 2001; **62**: 274–78.
- 29 Hegaard H, Hjaergaard H, Moller L, Wachmann H, Ottesen B. Multimodal intervention raises smoking cessation rate during pregnancy. *Acta Obstet Gynecol Scand* 2003; **82**: 813.
- 30 Chamberlain C, O'Mara-Eves A, Oliver S, et al. Psychosocial interventions for supporting women to stop smoking in pregnancy. *Cochrane Database Syst Rev* 2013; **10**: CD001055.
- 31 WHO. WHO recommendations for the prevention and management of tobacco use and second-hand smoke exposure in pregnancy. Geneva: World Health Organization, 2013.
- 32 Yu L, Hey E, Doyle L, et al. Evaluation of the Ages and Stages Questionnaires in identifying children with neurosensory disability in the Maggie Trial follow-up study. *Acta Paediatrica* 2007; **96**: 1803–08.
- 33 Jarvis MJ, Mindell J, Gilmore A, Feyerabend C, West R. Smoke-free homes in England: prevalence, trends and validation by cotinine in children. *Tob Control* 2009; **18**: 491–95.
- 34 Benowitz NL, Dempsey DA. Pharmacotherapy for smoking cessation during pregnancy. *Nicotine Tob Res* 2004; **6**: S189–OS202.
- 35 Gaysina D, Fergusson DM, Leve LD, et al. Maternal smoking during pregnancy and offspring conduct problems: evidence from 3 independent genetically sensitive research designs. *JAMA Psychiatry* 2013; **70**: 956–63.
- 36 Dubois J, Dehaene-Lambertz G, Kulikova S, Poupon C, Huppi PS, Hertz-Pannier L. The early development of brain white matter: a review of imaging studies in fetuses, newborns and infants. *Neuroscience* 2013; published online Dec 28. DOI:10.1016/j.neuroscience.2013.12.044.
- 37 Yang L, Chen L, Qiu X, et al. Fetal cerebral lobes development between 20 and 28 weeks gestational age: a postmortem MR study. *Int J Dev Neurosci* 2014; **32**: 23–27.
- 38 Anblagan D, Jones NW, Costigan C, et al. Maternal smoking during pregnancy and fetal organ growth: a magnetic resonance imaging study. *PLoS One* 2013; **8**: e67223.
- 39 Bublitz MH, Stroud LR. Maternal smoking during pregnancy and offspring brain structure and function: review and agenda for future research. *Nicotine Tob Res* 2012; **14**: 388–97.